REMARKS

Applicants gratefully acknowledge withdrawal of the 35 USC § 112, first paragraph, rejection (enablement) made in the Office Action mailed January 25, 2005.

The 35 USC § 101 Rejection

Claims 1-2, 5-6, 9, 13-28, 30-39, and 42-55 are rejected under 35 USC § 101, because the claimed invention allegedly lacks patentable utility. Specifically, the Office alleges that the claims lack either a specific or substantial utility. Applicants respectfully traverse the rejection.

Despite the fact that Applicants believe the Office has not made a *prima facie* showing of lack of utility, the Applicants provide the following discussion to assert the specific and substantial utility of the claimed invention.

Specific Utility

An invention has specific utility if the identified use is well-defined and has a particular benefit to the public and is specific to the subject matter claimed. As explained in the specification, one of the cardinal features of Alzheimer's disease (AD) is the deposition of plaques comprised of aggregated beta-amyloid peptides (Aβ) in the brain (specification at paragraph [07]). Aβ is produced from its precursor protein, APP, by proteolytic processing at its N and C termini by β- and γ-secretase enzymes, respectively (specification at paragraph [07]). Due to the critical role that β-secretase (e.g., BACE-1) plays in the onset, development, and maintenance of Alzheimer's disease, transgenic BACE-1 knockout animals, i.e., comprising at least one nonfunctional allele of a BACE-1 gene, are unique tools for the further study of Alzheimer's disease and particularly for the development of therapeutics to treat AD (specification at paragraph [61]).

Among other utilities discussed in the specification and in the previous responses dated October 28, 2004 and June 27, 2005, the claimed transgenic mice and cells have a well-defined use for determining the toxicity and/or side effects of BACE-1 inhibitors, which is particularly useful in the development of therapeutics for the treatment and/or

prevention of Alzheimer's disease. For example, transgenic mice that are homozygous for a defective BACE-1 allele can be used to assess whether the toxicity of an inhibitor is dependent on the inhibition of BACE-1 or on another biological mechanism. In other words, one can administer an inhibitor to the homozygous knockout mouse to see if it has any toxic effects other than what might result from the inhibition of BACE-1 (see paragraph [62]). It is not possible to observe such effect in "any animal", including an animal having wild-type BACE-1, as the Office asserts. Only the homozygous BACE-1 knock-out mouse would allow one to assess the toxicity effect of an inhibitor that is independent from the effect of BACE-1 inhibition.

Likewise, transgenic mice that are heterozygous for a defective BACE-1 allele are useful to assess the toxicity and dosage concerns of a BACE inhibitor. The heterozygous BACE-1 knockout mouse provides a model for testing the effect of inhibitors when less BACE-1 enzyme is present as a way of assessing dosage. For example, a particular dosage of inhibitor may not have an observable toxic effect in animals having a wild-type level of BACE-1, but the same dosage could show toxicity or an altered biological effect in animal having less BACE-1 enzyme or no BACE-1 enzyme. In having altered levels of BACE-1 enzyme, both the heterozygous and homozygous BACE-1 knockout mice are particularly useful for assessing the toxicity of a BACE inhibitor as well as assessing the dosage effects of an inhibitor.

The Office argues that the present claims lack specific utility because any animal could be used for any of the utilities argued by the applicants, including determining the side effects of a BACE-1 inhibitor. Applicants respectfully disagree. As explained above, transgenic homozygous and heterozygous BACE-1 knockout mice have altered levels of BACE-1 enzyme present and are thus useful for a toxicity analysis in a manner that is different from a toxicity analysis performed in animals having a wild-type BACE-1 gene.

Substantial Utility

A claimed invention has substantial utility if it defines a "real world" or "practical" use. According to the MPEP, "any reasonable use that an applicant has

identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility". MPEP §2107.01 I. The term "benefit to the public" is not interpreted "to mean that products or services based on the claimed invention must be 'currently available' to the public in order to satisfy the utility requirement." MPEP §2107.01, citing *Brenner v. Manson*, 383 U.S. 519, 534-35 (1966).

Although the Office argues that the present claims have no substantial utility, it fails to provide a reason why determining the side effects or toxicity profile of a BACE-1 inhibitor lacks real world use. For the reasons stated above, Applicants submit that the use of the presently claimed transgenic homozygous and heterozygous BACE-1 knockout mice and corresponding cells to determine the side effects a BACE-1 inhibitor is a practical use for determining the toxicity and dosage effects of a potential therapeutic for the treatment of AD.

For the reasons discussed above, the pending claims have specific and substantial utility. Accordingly, the Applicants respectfully request withdrawal of the 35 U.S.C. §101 rejection.

The 35 USC § 112, First Paragraph, Rejections

Claims 1-2, 5-6, 9, 13-28, 30-39, and 42-55 are rejected under 35 USC § 112, first paragraph, as allegedly failing to teach one skilled in the art how to make and use the claimed invention. Specifically, the Office alleges that since the claims are not supported by either a specific or substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. Applicants respectfully traverse the rejection.

For all of the reasons presented in previous responses and for all of the reasons discussed above, the specification clearly teaches one skilled in the art how to use the claimed invention. For example, the specification teaches that the presently claimed transgenic homozygous and heterozygous BACE-1 knockout mice and corresponding cells can be used to analyze potential side-effects (e.g., determine the toxicity profile) of

an inhibitor of beta-secretase by exposing the transgenic mouse to an inhibitor of beta secretase and measuring a change in the level of at least one component of the transgenic mouse wherein such change indicates a potential side effect. The specification further provides examples of methods that can be used to determine the toxicity profile (specification at, for example, paragraphs [28], [52], [62], and [77]).

In addition, the Office argues that claims 1-2, 5-6, 9, 13-28, 30-39, and 42-55 are not enabled because they contain subject matter which allegedly was not described in the specification in such a way to as to enable one skilled in the art to make and/or use the invention. Specifically, the Office asserts that the specification "states that the mice, methods and cells are for the identification of inhibitors of β-secretase and other proteases involved in A/β formation. However, ... the art at the time of filing did not teach that 'other proteases' were involved in A/β formation or involved in the onset of Alzheimer's disease." (Office Action pages 5-6). Applicants respectfully traverse the rejection.

First, the claims directed to transgenic mice and corresponding cells, as well as methods of making the mice (claims 1-2, 5-6, 9, 13-21, 27-28, 30-39, 42-53, and 55) do not recite a particular use and thus are not limited to the use of identifying inhibitors of β-secretase and other proteases involved in A/β formation. For example, the claimed transgenic mice and cells can be used to analyze potential side-effects (e.g., determine the toxicity profile) of an inhibitor of beta-secretase. As discussed above, the specification clearly teaches one skilled in the art how to use the transgenic mice and cells to analyze potential side-effects and determine toxicity of a BACE inhibitor. As long as the specification teaches at least one use of the invention, the enablement requirement is satisfied. Likewise, claims 25-26 are not directed to the use of identifying inhibitors of β-secretase and other proteases involved in A/β formation but rather are directed to methods of analyzing potential side-effects for an inhibitor of beta-secretase.

With respect to claims 22-24 and 54, which are directed to the use of identifying inhibitors of β-secretase and other proteases involved in A/β formation, the Office states that "the art at the time of filing did not teach that 'other proteases' were involved in A/β

formation or involved in the onset of Alzheimer's disease." Applicants respectfully disagree with the Office's assertion. At the time of filing, it was well-accepted in the art that Alzheimer's disease was associated with the over-production of A/β. Thus, proteases involved with the production A/β, such as the exemplary proteases discussed in the specification, were considered to be associated with Alzheimer's disease.

Specifically, the Office cites Hardy et al. to allege that the γ-secretase cleavage was not known to be due to a specific enzyme, but might be due to a single enzyme with less than perfect specificity. Contrary to the Office's argument, it was well-accepted in the art at the time of filing the instant application that γ-secretase protease activity was associated with A/β production and therefore associated with Alzheimer's disease. Regardless of whether the γ-secretase protease activity was the result of a single enzyme or more than one enzyme, the proteolytic activity of γ-secretase and its APP substrate site(s) were known and shown to be distinct from that of α- or β-secretases.

The Office also states that "wild type presenilin isn't associated with Alzheimer's disease." However, contrary to the Office's assumption, the teaching in the specification is not limited to "wild type presenilin". In fact, paragraph [7] of the specification teaches that mutations in APP, presenilin-1, and presenilin-2 genes result in the overproduction of A/β peptide and cause Alzheimer's disease.

Finally, the Office alleges that Farzan et al. teaches that "BACE-2 generated fragments have not been found in senile plaques associated with Alzheimer's disease" and thus BACE-2 is not implicated in Alzheimer's disease. The Office mischaracterizes the Farzan article by suggesting that Farzan teaches BACE-2 is not involved with Alzheimer's disease. In fact, Farzan teaches that BACE-2 may be involved in a specific type of Alzheimer's disease known as "familial Alzheimer's disease" associated with the Flemish mutation. Farzan concludes in his report that "these data suggest BACE-2 contributes to Aβ production in individuals bearing the Flemish mutation, and that selective inhibition of these highly similar proteases may be feasible and therapeutically advantageous." (p. 9712, Abstract)

Contrary to the Office's allegation, at the time of filing the instant application, proteases other than BACE-1, such as the proteases exemplified in the specification, were known in the art to be associated with A/β production and thought to be associated with Alzheimer's disease. Accordingly, the pending claims satisfy the enablement requirement and Applicants respectfully request withdrawal of the 35 USC §112, first paragraph, rejection.

CONCLUSION

In view of the above remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

Respectfully submitted,

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